PERIPHERAL PIGMENTATION OF THE CORNEÆ, ASSOCIATED WITH SYMPTOMS SIMULATING MULTIPLE SCLEROSIS.

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In 1902 Kayser referred to a peripheral annular pigmentation of each cornea in a patient whose nervous symptoms seemed to warrant a diagnosis of multiple sclerosis, and in the further course of the disease diabetes and pigmentation of the skin developed. Since the first report by Kayser, the histories of several other cases showing analogous ocular and nervous manifestations have been recorded. Recently the condition has been especially studied and discussed by Fleischer.

The clinical findings in the patient whose history is recorded below warrants the inclusion of this case in this particular group.

Mc G., aged twenty-seven years, was admitted to the University Hospital on the service of Drs. Charles K. Mills and William G. Spiller, December 12, 1912,[1] complaining of loss of control of his arms and voice.

History of Present Condition. The patient stated that he was perfectly well until the latter part of March, 1910, at which time he noted that the right hand would tremble and shake when he attempted to write. When writing it was necessary for him to steady the right hand with the left, and in a few months he was compelled to give up this method and do his writing with his left hand. In July, 1911, his voice became somewhat affected, so that he talked, as he expressed it, as "one who is afraid to speak." On December 25, 1911, he first became aware that the left hand was becoming affected in the same manner as the right. From that time on the tremor increased in extent and severity, until at the present time he is not able to button his clothes, brush his hair, or feed himself. This tremor disappears when he is quiet or after he has been in bed for a few minutes. In the summer of 1912 he first noticed that his head would start to shake, especially when he would talk. This also has increased in the past few months. For the past year there has been a jumping sensation in the muscles of his legs, as if they were contracting suddenly, but he has felt no loss of power, pain, or loss of control. This only occurs when he is lying in bed or sitting still, never when walking. Otherwise the patient feels perfectly well; he has not lost in weight; sleeps well; in fact, is rather drowsy all the time. He never has headache, but has some dizziness when rising from bed or from a stooping position. His appetite is good; his bowels, as a rule, are regular, but for the last month he has been somewhat constipated. There are no cardiac or respiratory symptoms.

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[1] This patient was first seen by me late in the summer of 1912, through the courtesy of Dr. A. C. Sautter. He was then under treatment at the German Hospital, and had been referred to the service of Dr. W. T. Shoemaker, for ocular examination, where he came under the observation of Dr. Sautter. He was exhibited at the April, 1913, meeting of the Philadelphia Neurological Society.

Previous Medical History. He has had the usual diseases of childhood. Since a boy he has been subject to vague rheumatic pains in the left arm and leg. No other sickness except gonorrhea a number of years go, which persisted for one year. He denies syphilis. He never sustained any injuries and never had any traumatic or inflammatory ocular condition.

Social History. He has been a painter for the last fourteen years, but has seldom used white lead, and none in recent years, his work calling for varnish. Mostly all of his work has been done in the open. He has used tobacco to excess. Since the summer of 1912 he has drunk very little, but prior to that he averaged seven or eight glasses of beer a day.

Family History. Negative. No history of nervous, cardiac, renal, or lung trouble.

Physical Examination. The patient is a large-framed individual, with good musculature; well nourished; no stigmas of hereditary lues. The face presents a distinctly dusky appearance, but the scalp is not affected. There is a suggestion of a fine capillarity over the cheeks and nose. On both legs over the anterior and outer surfaces there are large areas of brownish-yellow pigmentation, occurring in blotches. He thinks this has been present for about ten years. There are no evidences of edema. The skin is soft and moist. The peripheral arteries are not sclerosed. The pulse is slow and full and of fair tension.

Nervous System. The gait is normal. Station is good. There is a questionable tendency to Romberg's sign. The patellar, biceps, and triceps reflexes are somewhat exaggerated, but equal on the two sides. No ankle clonus; no Babinski sign. No change in the abdominal or cremasteric reflexes. There is no disturbance of sensation; the muscular power of the arms and legs is good. The tongue when protruded is not deviated to either side, but is accompanied by a slight tremor. The seventh nerve is intact. Speech is rather syllabic, slow, and deliberate. Heel-to-toe test is negative. Finger-to-nose test shows marked intention tremor. There is no propulsion or retropulsion. No dysphagia.

General System. The ears are apparently normal; the throat is negative; the teeth are poor; there is no blue line. The lungs, heart, liver, spleen, and abdomen are negative.

Ocular Examination. There is no true nystagmus, but at the extreme limits of the lateral rotations a faint nystagmoid jerk can be noted. The ocular rotations are not impaired. The pupils are larger than the average, but react promptly and normally to the various reflexes. By oblique illumination an annular pigmented zone can be noted about the periphery of the cornea of each eye, which produces a distinct contrast in color between the covered and exposed portions of the blue iris. With a Zeiss loupe there can be noted an annular pigmentation of the cornea which apparently involves the deepest layers. In the right eye this pigmented area is widest above and to the nasal side, and narrowest below and to the temporal side. The width of the involved area varies from 2 to 3½ mm. At the more peripheral portions it presents a smoky or brownish appearance, which fades into a brownish-green as the pigment disappears in the more central uninvolved portions of the cornea. The apparently clear central portion of the cornea is oval. With a Nernst lamp and a Zeiss corneal microscope there is a suggestion of a finely granular appearance toward the limbus, but this is not pronounced. The cornea is not vascularized, nor does it show any opacities that might be the result of congenital or inflammatory conditions. No pathological changes could be seen in the iris. With the opthalmoscope no opacities were seen in the lens or vitreous. The disks were nearly round, suggestive of a reddish-gray type, but no pallor of the temporal sector was seen; no evidences of neuritis. There were no vascular changes, and the choroid and retina were healthy. The fields for form and colors were normal, and no scotoma could be elicited either by the ordinary perimetric examination or by Bjerrum's method.

O. D. = .50 pp. 13.5 cm., with + .25 cyl. ax. 180 = $\frac{6}{5}$ +.
O. S. = .50 pp. 13.5 cm., with + .25 cyl. ax. 165 = $\frac{6}{5}$ +.

Progress of the Case.—December 16, 1912. Urine: cloudy and straw colored; sp. gr., 1011; alkaline; faint trace of albumin; sugar negative; bile, urobilin, and indican negative; casts, mucus, and red-blood corpuscles negative; occasional white corpuscles; amorphous phosphates and urates.

Blood. Red corpuscles, 4,330,000; white corpuscles, 7100; hemoglobin, 75 per cent.; polynuclear, 65; lymphocytes, 28; transitional, 2; eosinophiles, 5.

Blood Pressure. Systolic, 125; diastolic, 80.

Levulose Test. December 19: 65 grams of levulose in 200 c.c. of water were given on a fasting stomach and the urine collected every hour for five hours. Except for the third-hour test, which was spoiled, a positive reaction was obtained for each examination. (Dr. F. G. Sproul.)

Wassermann Test. Negative.

December 21. Examination by Dr. O. H. P. Pepper confirmed the above findings, but owing to several punctate bluish granules at the gum margin an examination for degeneration of the red cells was suggested. A slight cervical adenopathy was noted.

Feces. Light brown, semisolid; no fat or mucus; occult blood negative; slight trace of bile; plant cells, muscle fibres, epithelium, leukocytes, bacteria, yeasts, crystals, and debris.

Blood examination for basic degeneration was negative.

December 23. Stomach contents: specimen a creamy, turbid fluid, with granular sediment and brown specks. Free HCl, 60 per cent. (dimethylamidobenzol); total acid, 75 per cent.; lactic acid, 0; occult blood, negative; starch, yeast, bacteria, leukocytes, Oppler-Boas were negative.

February 6, 1913. Levulose test by Dr. J. Gordon Saxon: With 40 grams of levulose a typical reaction to resorcin was obtained for six hours; this was confirmed by spectroscopic examination. With 30 grams of levulose there was a similar result.

March 16. A test for increased sympathetic tonus was made by Dr. Arthur Hopkins and gave a positive result. A hypodermic ingection of ten minims of adrenalin (1 to 1000) was given and the case observed during the following hours. The blood-pressure was raised 18 points; marked tremor provoked; sugar tolerance markedly reduced and lymphocytes increase by 13 per cent.

A Röntgenogram of the head by Dr. H. K. Pancoast was negative.

May 4. Hemoglobin, 70 per cent.; red-blood cells, 4,050,000; white-blood cells, 7000.

During the several months the patient was under observation there was an improvement in his tremor, but aside from this there was practically no change. The station and gait remained normal, and no psychic phenomena developed. Drs. Hartzell and Knowles, who examined the skin lesions, reported a colloid degeneration of the skin of the forehead and a mild type of acne rosacea associated with a pigmentation of the legs, due to blood pigment, which occasionally follows erythematous eczema.

In 1910,[2] in an article on corneal pigmentation, I had occasion to causually refer to this particular type of pigmentation, but at that time I had never observed a case, and had overlooked a contribution to this subject by Fleischer in 1909.[3] This observer has especially studied the few cases of this character that have been observed or at least recorded, and has had opportunities to study the two cases that have come to autopsy, so frequent references will be made to his findings. Since I could find references to but five cases that exhibited this type of corneal pigmentation it may be well to review these histories.

In 1902 Kayser[4] reported from the Tübingen Clinic the history of a male, aged twenty-eight years, who for five years had what was regarded as multiple sclerosis. While the patient was not regarded as a confirmed alcoholic, the first symptoms developed after alcoholic excesses. In each eye there existed an annular peripheral pigmentation of the cornea, which began at the limbus and gradually faded away centrally, so that a central oval area of the cornea remained normal. The widest part of the pigmentation was above and below, more in the former position. Examination with the Zeiss microscope did not reveal any abnormalities at the limbus or in the cornea itself, other than the pigmentation, which was dense enough to obscure the iris. The peripheral portion was noted to be made up of an accumulation of yellowish granules, which became finer and more diffuse centrally where the color changed to yellowish-green. This pigmentation was observed to be deep; the superficial and middle layers of the cornea were not affected. Fleischer had further opportunities to study this patient, and has reported on the later findings.[5] The patient was intermittently under observation up to the time of his death in May, 1909. During this period the nervous phenomena became worse, distinct psychic phenomena occurred, while late in the course of the disease there developed diabetes and a grayish-brown pigmentation of the head and hands, with grayish discoloration over the chest and abdomen. The liver was palpable, but not the spleen. There was no reduction in the visual acuity, but the pigmentation of the cornea increased, and there was some lessening of the light sense.

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[2] Annals Ophthal., 1910, xix, 685.

[3] Münch. med. Woch., 1909, p. 1121.

[4] Klin. Monatsbl. f. Augenheilk., 1902, xl, ii, 22.

Autopsy. The liver was rather small and nodular, the spleen enlarged, and the kidneys pigmented. There was a small localized patch of thickened pia near the vertex. Macroscopically and microscopically there were no signs of multiple sclerosis. Microscopically the cornea showed a pigmentation of Descemet's membrane that extended centrally about 1.9 mm. The deposit consisted of rounded and angular greenish-brown granules that appeared refractile at a certain angle. This deposit was separated by a clear space from the endothelial cells, which were normal in appearance. The only other structure of the eye that presented any pigmentation was the hyaline membrane of the choroid or the membrane of Bruch. Here the deposit was more marked than in Descemet's membrane, and the granules finer than in the adjacent pigment epithelium and the pigment cells of the choroid. The interstices and fibres of the eye muscles were pigmented, as was the optic sheath, but the nerve itself was free. In the kidneys the basement membrane of the urinary tubules were especially pigmented. In the liver the pigment was found in the interacinal connective tissue. There were evidences of degeneration of the liver cells and proliferation of the connective tissue. The spleen was markedly pigmented, especially in the trabeculæ and walls of the bloodvessels, and also in the pulp, but here it was mostly extracellular. In the intestines the pigment was present in the vessel walls and in the circular muscle. The connective tissue of the heart was pigmented, while in the skin the basal layer of epithelium was affected, also the connective tissue of the hair follicles and the basement membrane of the sweat glands. The pia was pigmented, but the lungs were free. The adrenals were normal. The condition of the pancreas was not described.

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[5] Bericht der Ophthalmologischen Gesellschaft, Heidelberg, 1908, p. 128.

In the following year Fleischer[6] at the same clinic observed two similar cases. This first patient was a male, aged twenty-nine years, with a kyphosis. Venereal disease was denied and there was no history of alcoholism. The patient had a high hyperopia, congenital amblyopia, and horizontal nystagmus. Nervous symptoms in the form of an intention tremor first appeared a year before. This patient had the same type corneal pigmentation as above described. His neurological condition was regarded as pseudosclerosis. The patient later developed distinct psychic changes and an intermittent glycosuria. He died in February, 1906.

Autopsy. The consistency of the liver was increased, its surface nodular, and on section, increase of the connective tissue was noted. There were evidences of slight chronic emphysema and bronchitis. The cardiac muscle showed some degeneration, the left ventricle was hypertrophied and the aorta and coronary arteries were atheromatous. The spleen was enlarged. In the stomach there was a copious hemorrhage and the scar of a cicatrized ulcer. In the brain the lateral ventricles were dilated, there were evidences of a chronic external pachymeningitis and chronic leptomeningitis, but discolored sclerotic patches or focal brain lesions were not found. No mention was made of the condition of the adrenals or pancreas, and no microscopic examination was made.

The second case was a male, aged thirty-one years. The left eye had been enucleated, owing to severe corneal ulceration secondary to dacryocystitis, but unfortunately no microscopic examination had been made. The right eye presented the type of corneal pigmentation now under discussion. Nervous symptoms had existed for two or three years, and were attributed to multiple sclerosis.

The fourth case was observed by Salus.[7] The patient was a male, aged thirty-two years, who had been affected with nervous symptoms for a number of years. When seen in February, 1908, there was noted an annular brownish-green pigmentation of the corneæ, which presented a granular apearance when studied with the Zeiss microscope. The neurological condition was regarded as multiple sclerosis.

At the conclusion of Fleischer's[8] most recent article he has briefly referred to a fifth case that has been observed by Gallus, as well as Westphal.[9] This patient was a girl, aged nineteen years, who had greenish discoloration of the corneæ and a tremor resembling that seen in pseudosclerosis, but up to the time of his report no discoloration of the skin or diabetes had developed.

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[6] Klin. Monatsbl. f. Augenheilk., 1903, xli, p. 489.

[7] Medizinische Klinik, 1908, iv, 495.

[8] Deutsch. Zeitsch. f. Nervenheilk., 1912, xliv, 179.

Among the patients so far affected all have been young adults, and five of the six patients were males. Several of the case histories make reference to preceding rheumatic affections or pains in the extremities and in one case there existed prolonged gastric disturbance some time prior to the onset of the disease. In Kayser's case the symptoms first developed after alcoholic excesses; Salus' patient attributed his to exposure to cold. No probable cause could be found for the other cases. The fact that the patient whose history is above recorded was a painter seems to be significant, but he used lead but little in his work, and not at all for the past few years; there was no history of colic and no basic degeneration of the red cells. He was, however, a consistent beer-drinker, and in the use of varnishes would be exposed to methyl alcohol; however, there is no history or ocular indications of any acute intoxication from this latter substance, but the possibility of some influence brought about by the frequent use and handling of this substance cannot, of course, be denied. The most conspicuous symptom and the one that has been constant in all the cases has been the marked coarse intention tremor affecting the arms and head in all cases, and in some the lower extremities as well. In Fleischer's first case and in the one here recorded the gait was normal, but in the others it became rather spastic. In all of the cases the cranial nerves were normal. Fleischer in speaking of Kayser's case states that the speech was not scanning in type, but owing to the tremor it was difficult; in the patient whose history is here recorded the speech was certainly affected more than could be accounted for by the tremor alone, and further no change was noted when the patient was quiet. Kayser's and Fleischer's first patient were the only ones to develop psychic phenomena, and in each instance this change was pronounced. The knee-jerks were exaggerated in Kayser's and Fleischer's second case, as well as in the case above mentioned, but in Fleischer's first case they were normal. In Salus' case they were absent. Ankle clonus was intermittently present in Kayser's case; Salus does not refer to it; while in the other cases it was absent. The abdominal and cremasteric reflexes were absent in Salus' case and were affected late in Kayser's case; in the other cases no change was observed. Salus does not refer to Babinski's sign, but in the other cases it was absent. In Kayser's case the head and hands presented a grayish-brown pigmentation of the skin, while there was some grayish discoloration over the chest and abdomen. While I did not find any reference to skin pigmentation in the history of Salus' case, Fleischer states a brownish pigmentation of the head was observed. The condition of the face and legs in the case here recorded has been referred to above. Glycosuria has been observed twice, and in a third case, while there was no glycosuria, there did exist a decided reduction in the sugar tolerance.

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[9] Since forwarding this manuscript to the editor, I have found reference to a recent article by Westphal (Archiv f. Psychiatrie und Nervenkrankheiten, 1913, li, Heft 1), but at the present writing the original is not available.

All of these cases showed the same type of cornea pigmentation. A deep annular pigmentation beginning at the limbus, appearing brownish green in color, and in its denser peripheral portion presenting a "smoky" appearance. It can readily be overlooked, and in brown irides would be especially difficult to detect, even by a trained observer. It is also well masked by a mydriatic, owing to the retraction of the iris behind the pigmented area. Its true character can only be detected with a loupe. Aside from the pigmentation it can be said that in all cases the eyes were negative, and did not show the changes so frequently present in cases of true multiple sclerosis. The vision remained unaffected.

In the two cases that have come to autopsy there existed a cirrhosis of the liver, associated with splenic enlargement and other changes already alluded to.

REMARKS. The diverse and complex character of the symptoms exhibited by the patients who have shown this type of corneal pigmentation makes the study of this group of cases most interesting. Kayser at the time of his report regarded the pigmentation of the cornea as congenital. Fleischer in the following year, while he called attention to the association of the corneal condition with symptoms of multiple sclerosis, was doubtful of their direct connection, although he did not exclude the possibilities of the pigmentation being an acquired condition. In a later brief reference[10] to it he stated that he believed it to be in some way connected with the debilitated condition of the patients. Salus believed the neurological condition to be multiple sclerosis, and suggested that Fleischer's case, regarded as pseudosclerosis, was also one of multiple sclerosis, and he believed there was an undoubted connection between the corneal pigmentation and the nervous symptoms. He called attention to the fact that the pigmentation most closely resembled blood-staining of the cornea, and based his suggestion on the work of Lapinski in reference to degeneration of the vessels in lesions of the sympathetic, he thought it possible that owing to innervation disturbances in the canal of Schlemm there resulted a slow filtration from this canal and imbibition of the coloring matter of the blood by the deeper layers of the cornea. While the incomplete autopsy on Fleischer's case in 1906 gave some suggestion of the complex character of some or possibly all of these

[10] Klin. Monatsbl. f. Augenheilk., 1908, xlvi, 91.

cases, it was not until opportunities were offered for more careful study in the case first observed by Kayser that a pigmentation of the internal organs was definitely demonstrated. Fleischer has made a most painstaking study of this case, and in his recent able contribution has discussed the various phases of the conditions presented.

Since in both of the cases that came to autopsy there had existed a glycosuria, with the postmortem findings of cirrhosis of the liver and enlarged spleen, associated with marked widespread pigmentation of the internal organs in the one case, and in the other (Fleischer's) the macroscopic examination intimate the possibility of analogous pigmentation, the possibility of a hemochromatosis or bronzed diabetes was immediately suggested.

The pathogenesis of hemochromatosis is still obscure. Probably the most prevailing opinion is that the pigmentation is the primary condition; Letulle[11] has regarded the diabetes as the original factor, while Potter and Milne[12] state that "it would seem as if today we are warranted in stating only that cirrhosis of the liver is the primary condition; that the hemochromatosis, always in slight degree in liver cirrhosis, is in some cases very excessive, and causes a general pigmentation which eventually also involves the skin; and finally, that the whole process is not any definite symptom-complex, but a chain of circumstances which rarely seems to be completed." On the other hand, Sprunt,[13] supporting the opinion of Opie,[14] regards it as a distinct morbid entity, and states there is no evidence of any abnormal blood destruction. He considers it a metabolic disease, "manifested, especially, by a change in the chromogenic groups of the proteid molecule with the deposition of pigments, and believes that the fibrosis of the various organs is dependent upon pigmentary degeneration and the accumulation of pigment in the interstitial tissue.

In the case so thoroughly studied by Fleischer, instead of finding the iron-containing hemosiderin and the iron-free hemofuscin, which characterize cases of hemochromatosis, he found a pigment that did not give the usual reactions of these pigments, and its exact character has not been definitely determined, although he believes the pigment to be a blood derivative. For the exact chemical properties of the pigment found, the reader is referred to Fleischer's recent article. Owing to the conflicting reports concerning the character of the pigment present in this case, its careful study has added but little if any to our meager knowledge concerning the physiological and pathological body pigmentations.

While this group of cases has certain symptoms in common with those found in hemochromatosis, reference to some of the more convenient articles bearing on the latter subject, such as those contributed by Opie, Blumer,[15] Potter and Milne, and Sprunt, failed to reveal any reference to cases associated with nervous phenomena such as characterized these cases, and no reference is made to any corneal pigmentation that has been observed; on the other hand, Fleischer shows that the ocular microscopic findings are quite different.

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[11] Cited by Potter and Milne.

[12] Amer. Jour. Med. Sci., January, 1912.

[13] Archives of Internal Medicine, 1911, viii, p. 75.

[14] Trans. Assoc. Amer. Phys., 1899, xiv, 253.

This same observer also considered the possibility of poisoning by various metals especially silver, and pointed out certain resemblances to cases of manganese poisoning. As to the latter substance, this can be definitely excluded in the case here recorded, by the history, and I dare say the same is true about the other cases in this group. Casamajor[16] has recently referred to 9 cases of possible manganese poisoning, and has reviewed the literature. In the one case of his series that came to autopsy a superficial inspection of the brain-stem blocks before embedding, suggested the possibility of slight changes about the lenticular nucleus.

As to silver, while a chemical examination of small pieces of the kidney and spleen in Fleischer's case seemed to show the presence of this metal, certain other tests seemed to make this improbable, and it was further pointed out that there was no history of the patient having taken silver; that in argyrosis no such nervous and pcyshic symptoms develop, nor is the pia pigmented. It was also stated that the cornea is never involved in argyrosis. While this may be the case after argyrosis produced by the ingestion of silver, Knies[17] has referred to a brownish pigmentation of the cornea after cauterizations with silver nitrate stick. In this case the corneal epithelium and endothelium were not involved, but the stroma, Bowman's membrane and Descemet's membrane, were pigmented, as were the large deep lymph spaces and the four straight eye muscles.

In the case studied by Fleischer, the pigment, so far as the eye was concerned, seemed to have a selective action affecting two of the three important hyaline membranes of the eye, the membranes of Bruch and Descemet, both of which contain elastic fibres. The exemption of the lens capsule was explained by him as due to difference in chemical properties.

Fleischer has also considered pseudosclerosis and diffuse cerebral sclerosis. Oppenheim[18] and Potts and Spiller[19] refer to the difficulties attending the diagnosis of pseudosclerosis, while Wilson is still more emphatic and thinks the term should be abandoned.

Volsch[20] has placed on record the history of a case that he believed to be analogous to Fleischer's, and has seen fit to group these with certain other cases attributed to pseudosclerosis. In his case there was also a cirrhosis of the liver, but no pigmentation of the cornea or internal organs. While corneal pigmentation was not especially sought for, he thinks it unlikely that this could have been overlooked. Wilson,[21] in an admirable monograph, has recently called attention to a definite syndrome occurring in the course of progressive lenticular degeneration, which he describes as "a disease which occurs in young people, which is often familial, but not congenital or hereditary; it is essentially and chiefly a disease of the extrapyramidal motor system, and is characterized by involuntary movements, usually of the nature of tremor, dysarthria, dysphagia, muscular weakness, spasticity, and contractures with progressive emaciation; with these may be associated emotionalism and certain symptoms of a mental nature. It is progressive and, after a longer or shorter period, fatal. Pathologically it is characterized predominantly by bilateral degeneration of the lenticular nucleus, and in addition cirrhosis of the liver is constantly found, the latter morbid condition rarely if ever giving rise to symptoms during the life of the patient." In the four personal observations of the author careful ocular examinations were evidently made, in the other case histories reviewed by him, eight in all, the ocular reports were incomplete or wanting, but in no case was there any reference to a pigmentation of the cornea, and the eyes were normal in other respects as well. All of the cases that came to autopsy had a marked cirrhosis of the liver, but nowhere in his careful and elaborate reports does he refer to any pigmentation of the internal organs. Wilson thinks that in connection with the hepatic cirrhosis, which does not produce any clinical signs during the life of the patient, a toxin is probably generated which exerts a selective action on the cells and fibres of the lenticular nucleus. In the addendum he alludes to Volsch's case, and believes it belongs in the group of cases he has so carefully described. He also refers to Fleischer's case, but makes no positive statement in regard to it, although the inference is that he would similarly classify it.

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[15] Yale Med. Jour., 1912, xviii, 190.

[16] Jour. Amer. Med. Assoc., 1913, lx, 647.

[17] Klin. Monatsbl. f. Augenheilk., 1880, xviii, 165 (cited by Parsons, The Pathology of the Eye) Jahresbericht f. Ophthal., 1880, 194.

[18] Text-book of Nervous Diseases, translated by Alexander Bruce.

[19] Jour. Amer. Med. Assoc., 1905, xlv, 1455.

[20] Deutsch. Zeitsch. f. Nervenheilk., 1911, xlii, 347.

In the patient whose history is here reported the essential signs and symptoms have been the tremor, the character of the speech, and the corneal pigmentation. While no glycosuria manifested itself, there existed a marked reduction in the sugar tolerance. As above noted, the skin lesion of the face was attributed to acne rosacea, while the yellowish-brown pigmentation of the legs was said to be due to blood pigment such as at times follows erythematous eczema.

It is at least interesting to note the marked positive reaction this patient gave to the test for increased sympathetic tonus, the tremor being most markedly exaggerated for a period of two days. In this country Barker[22] and Hopkins[23] have referred in detail to the vagotonic and sympathicotonic states, and I am much indebted to the latter observer for his interest in the present case. While our present knowledge of the so-called autonomic and sympathetic systems may not warrant our drawing any definite conclusion, the results are none the less interesting, especially in cases of this character where the pathogenesis is obscure and unknown.

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[21] Brain, 1912, xxxiv, 295.

With the uncertain results in the chemical and microchemical tests in the case studied by Fleischer, considering the opinion expressed by Wilson, and the absence of pigmentation in the cases studied by him, as well as in the case referred to by Volsch, one may well ask whether we are really dealing with an acquired pigmentation of the cornea that has any connection with the other symptoms noted in these cases?

Concerning this it may be pointed out that in the 6 cases that have shown corneal changes the pigmentation has been bilateral; the cornea and the intra-ocular structures have been free from evidences of any traumatic or inflammatory condition apt to be associated with corneal pigmentation. But excluding a high refractive error and squint that were present in one case, other defects or anomalies that might be regarded as congenital have been wanting, unless, despite two autopsy reports, we regard the neurological symptoms as dependent upon a true multiple sclerosis, and accept the views of Strümpell, Ziegler, and Müller[24] that this affection is due to a congenital tendency to proliferation of the glial tissue. While all of the cases except one (Salus) exhibited this type of pigmentation when they first came under observation, all of them had been otherwise affected for a year or more. None of these cases had conical cornea, and, at any rate, there is practically no resemblance between this and the superficial annular pigmentation described by Fleischer and Hudson[25] as having been observed in cases of keratoconus. In one case (Kayser's) the pigmentation was said to have increased while the patient was under observation. To the best of my knowledge corneal changes of this character have not been observed or at least recorded except in association with the symptoms noted in these patients. Even if one accepts the report of the presence of silver (kidney and spleen) in Fleischer's case and eleminates the possibility of an associated pigment, it is hardly reasonable to suppose that all six of these cases had argyrosis.

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[22] Trans. Assoc. Amer. Phys., 1912.

[23] Preliminary report read before the Section of Medicine, College of Physicians of Philadelphia, February, 1913.

[24] Cited by Oppenheim, Text-book of Nervous Diseases, translation by Alexander Bruce, vol. i, p. 333.

[25] Royal London Ophthalmic Hospital Reports, 1911, xviii, 198.

In the absence of more definite data concerning the character of the pigment it is futile to speculate as to the manner in which the eye structures become affected; at any rate, the study of cases of true hemochromatosis has still left the question of the formation and possible transporation of the pigment an open one. Since the publication of Wilson's observations and deductions, cases of this character will be watched with additional interest, and in turn it is hoped that in the study of certain clinical conditions already mentioned, the possibility of corneal pigmentation will be borne in mind.

From the study of these cases we can only conclude that in association with certain symptoms, of which a coarse intention tremor affecting the extremities and head is the most conspicuous, there may develop a deeply seated annular brownish-green pigmentation of the cornea. That some or possibly all of these cases are associated with a cirrhosis of the liver, which has been shown to exist in 2 cases. That during the course of the disease a glycosuria or a lowering of the sugar tolerance may develop. Accepting the autopsy findings in 2 cases and the neurological opinions expressed on the case whose history is here reported, the nervous manifestations are not due to multiple sclerosis.[26]

In conclusion, I gratefully acknowledge the courtesty extended by Drs. Mills, Spiller, and de Schweinitz for placing this patient at my disposal for clinical observation.

INFANTILISM.

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The name infantilism was coined by Lasègue, who designated by it the persistance of childish characteristics, physically as well as psychically, into adult life. With the increasing knowledge of various clinical pictures the term underwent modifications, having been circumscribed by different authors in varying ways. A great impetus was given to the studies of the various forms of retarded and checked development by the investigations of the functions

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[26] Since this manuscript was forwarded to the editor, Rumpel (Deutsch. Zeitsch. Nervenheilkunde, 1913, xlix, Heft 1 u. 2, S. 54) has referred in detail to the character of the liver changes and the pigmentation. He believes the hepatic changes depend upon a faulty fetal development which results in a functional insufficiency that gives rise to disturbances of metabolism and auto-intoxication, and that this is responsible for the neurological symptoms. The pigmentation he regards as an argyrosis.